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Short communication

The use of nasal calcitonin spray in the treatment of hypercalcaemia of malignancy

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Introduction

Hypercalcaemia is a frequent metabolic complication of advanced malignant disease. Calcitonin has been shown to be effective both in controlling malignant hypercalcaemia [10] and in reducing pain in patients with bone metastases [9]. A number of other treatments are also effective in reducing serum calcium levels in malignant disease, including mithramycin [5], intravenous phosphate infusions [2] and bisphosphonates [1]. All effective preparations currently used in managing acute malignant hypercalcaemia require parenteral administration. Synthetic salmon calcitonin has recently been formulated as a nasal spray, and we report on its use in the treatment of hypercalcaemia of malignancy.

Patients and methods

A total of 14 patients with advanced malignant disease and associated hypercalcaemia were studied. All subjects had been optimally hydrated with intravenous fluid prior to study entry and exhibited ionised serum calcium concentrations of >1.4 mmol/l at entry (mean, 1.601 ± 0.097 mmol/l; 95% confidence interval, laboratory reference range, 1.19–1.38 mmol/l). Two patients had myeloma, one had squamous-cell lung cancer and the remainder had breast cancer. No subject had received treatment for hypercalcaemia within 4 weeks of study entry, although three were undergoing long-term diuretic therapy and one was receiving a maintenance dose of corticosteroids. All patients gave informed consent and the study was approved by St. George's Hospital Ethical Committee.

Synthetic salmon calcitonin was given as a nasal spray (SMS 20-051 NS, Sandoz) delivering either 100 or 200 IU in 0.09 ml per actuation. The initial group of eight patients were treated with an escalating dose regimen as follows: 400 IU at 1000 hours on day 1, 200 IU at 1000, 1400 and 2200 hours on day 2, and 400 IU at 1000, 1400 and 2200 hours on all subsequent days. The second group of six patients received 800 IU at 1000, 1400 and 2200 hours on each day of the study. Serum ionised calcium was measured at 1000 and 1600 hours on each study day. Serum ionised calcium levels were also measured over a 24-h period at 1000, 1600, 2200 and 1000 hours in seven normocalcaemic patients with advanced malignant disease to determine the diurnal variation of this parameter.

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Results

Escalating dose regimen

A sustained fall in ionised serum calcium was documented in 2/8 patients, only 1 of whom showed levels within the normal range after 5 days of intranasal calcitonin administration. In both responders there was a progressive hypocalcaemic effect after successive doses of calcitonin.

Fixed-dose regimen

3/6 patients treated with 800 IU three times daily displayed sustained falls in ionised serum calcium levels. However, in none of these responders did the concentration achieved after 4 days fall within the normal range. No significant benefit was obtained from this higher-dosage regimen in terms of either response rate or average fall in ionised calcium. Intranasal calcitonin was tolerated well by all 14 patients, who exhibited no side effects during this study.

Diurnal variation in ionised calcium

Seven normocalcaemic cancer patients displayed a diurnal variation in serum ionised calcium levels, with morning peaks falling to late afternoon troughs and then recovering overnight. The mean circadian fall in ionised calcium observed in these subjects between 1000 and 1600 hours was 0.019 ± 0.012 mmol/l ($P > 0.05$). In comparison, all eight patients given an initial dose of 400 IU calcitonin at 1000 hours demonstrated a greater decrease in serum ionised calcium over the same period (mean fall, 0.099 ± 0.019 mmol/l; $P < 0.01$) and a subsequent nocturnal increase. This marked diurnal variation in serum

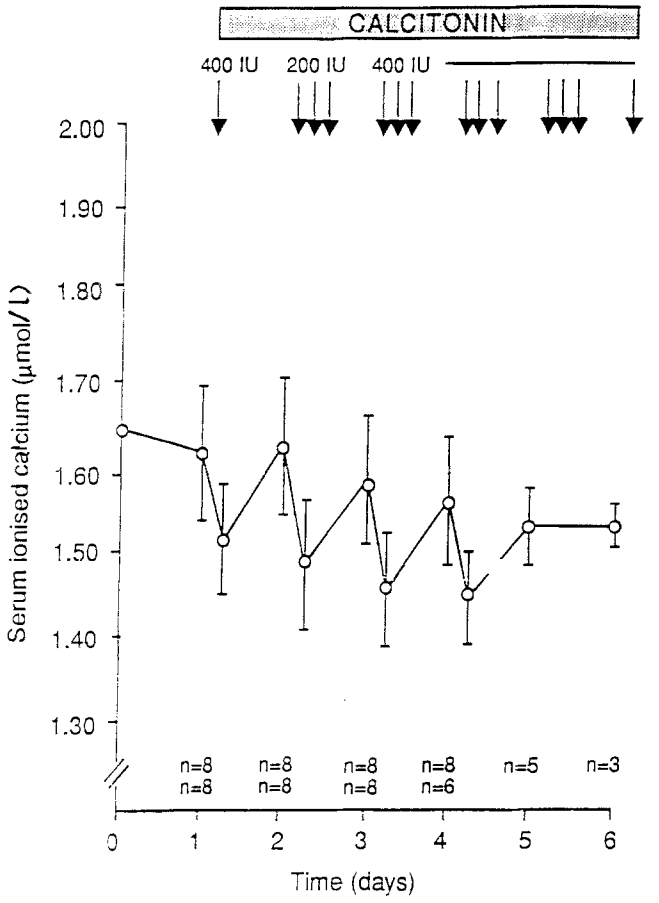

Fig. 1. The effect of mean serum levels of ionised calcium produced by escalating the dose of calcitonin to a maximum of 400 IU three times daily in 8 patients (bars represent the SEM)

levels of ionised calcium persisted throughout the study in the calcitonin-treated hypercalcaemic patients (Fig. 1).

Discussion

Salmon calcitonin delivered by nasal spray produced a sustained fall in serum calcium levels in only a minority of patients with malignancy-associated hypercalcaemia. The absorption of nasal calcitonin is variable [6], but the advantages of this route of administration as compared with parenteral therapy are obvious. It is most suitable for maintenance therapy rather than for in-patient management of acute hypercalcaemia due to convenience of intranasal administration. Our data suggest that intranasal calcitonin therapy using the present formulation is not of major efficacy in the management of acute hypercalcaemia. Despite the disadvantages of variable absorption and limited efficacy, the role of maintenance treatment with nasal calcitonin in responsive patients merits further investigation, as such treatment may be a useful adjunct to oral bisphosphonate maintenance therapy.

In normal humans a circadian variation in serum levels of ionised calcium has been documented, displaying a mid-morning peak and a subsequent decrease to a late afternoon nadir [3, 4]. The present study demonstrated that these diurnal rhythms also occur in normocalcaemic cancer patients. The same diurnal pattern of ionised serum calcium was demonstrated in hypercalcaemic subjects who were treated with calcitonin, but the fluctuations were more marked. The circadian variation of serum levels of ionised calcium in untreated hypercalcaemic cancer patients is unknown, but the exaggeration of the pattern in our patients may either reflect their underlying rhythm or be an effect of calcitonin.

Hypercalcaemia in malignant disease arises by two known mechanisms: (1) parathyroid hormone-related peptide secreted by tumours increases renal tubular reabsorption of calcium, and (2) cytokine production by bone metastases leads to local osteolysis and increased calcium release from bone [11]. Bisphosphates act predominantly to prevent bone reabsorption, whereas calcitonin functionally antagonises parathyroid hormone-related peptides. The combination of parenteral bisphosphate and calcitonin produces rapid and prolonged suppression of malignant hypercalcaemia [7]. Oral etidronate disodium maintained normocalcaemia in 35% of patients who had been treated for malignant hypercalcaemia [8]. The addition of nasal calcitonin to this maintenance therapy may increase its efficacy without producing additional toxicity or the need for parenteral administration. Further studies are required to address the role of this product in maintaining normocalcaemia.

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